Journal of Clinical Anesthesia 107 (2025) 112009

Contents lists available at ScienceDirect

Journal of Clinical Anesthesia

journal homepage: www.elsevier.com/locate/jclinane

Review

Tissue perfusion as the ultimate target of hemodynamic interventions in the perioperative period

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HIGHLIGHTS

- Vasodilation is essential for increasing local tissue blood flow and ensuring adequate oxygen delivery.
- Anesthesia affects both tissue metabolism and perfusion, altering normal physiological responses.
- Increasing blood pressure or cardiac output does not always translate to better tissue perfusion.
- Monitoring tissue perfusion could help evaluate the true effectiveness of hemodynamic therapy during surgery.

ARTICLE INFO

Keywords:
Tissue perfusion
Perioperative care
Goal-directed therapy
Intraoperative hypotension

ABSTRACT

This point-of-view article examines the complex relationship between global hemodynamic parameters and tissue perfusion, emphasizing the limitations of using macrohemodynamic metrics as proxies for tissue-level oxygen delivery. Key topics of the paper include the physiological determinants of tissue perfusion, the influence of anesthesia on perfusion dynamics, and the role of hemodynamic interventions in optimizing perfusion. Furthermore, we explore the application of tissue perfusion monitoring in the perioperative setting, highlighting its potential to guide individualized therapies. By addressing these interconnected factors, we advocate for further research to evaluate whether adding perfusion-guided strategies to current protocols can enhance patient outcomes.

1. Introduction

Hemodynamic interventions aimed at improving postoperative outcomes have been the purpose of many clinical trials in the past decades. Special attention has been given to goal-directed therapy (GDT), which is a clinical approach aimed at optimizing cardiovascular status by targeting specific parameters such as cardiac output (CO) as the major determinant of oxygen delivery (DO2) to the tissues [1]. Furthermore, numerous trials with perioperative vasopressor use were conducted to increase blood pressure and consecutively decrease related organ damage [2]. Although macrohemodynamic optimization has shown benefits in some perioperative settings, results across trials have been heterogeneous, and in many cases, outcome improvements were modest or absent [2–4]. It has been speculated that this is mainly due to the one-size-fits-all approach that may not fulfill personalized medicine principles, in which each patient exhibits unique characteristics and may respond differently to the same intervention [5–7]. Evidence, mainly derived from critical care trials, suggested that hemodynamic optimization tailored by assessing tissue perfusion, is a rational, more individualized therapeutic strategy. Indeed, maintaining tissue perfusion, and thus oxygen delivery, is the ultimate role of the cardiovascular system (CVS) [8–10]. Unfortunately, sole reliance on macrohemodynamic parameters as proxies for tissue perfusion has been proven to be suboptimal, as they may not reflect metabolic demands of

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https://doi.org/10.1016/j.jclinane.2025.112009
Received 23 February 2025; Received in revised form 26 July 2025; Accepted 9 September 2025
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the tissues [11]. This can lead to interventions that, while achieving certain macrohemodynamic goals, do not adequately augment tissue perfusion [12]. Additionally, these interventions may entail complications, compromising patient outcomes [2,13].

This point-of-view paper explores the relationship between global hemodynamics and tissue perfusion, delves into the mechanisms regulating tissue perfusion, and emphasizes the need for more nuanced monitoring strategies to assess the true impact of hemodynamic interventions during the perioperative period.

2. Physiological determinants of tissue perfusion

Perfusion of the tissues is driven by their metabolic needs. This dogma is clearly visible in vivo in the skeletal muscles, where in rest, blood flow is around 3 mL/min per 100 g, and can increase up to 60 mL/min per 100 g (20× increase) during exercise [14,15]. To sustain the tissue function, the increased oxygen demand (↑ metabolism) must be coupled with increased oxygen delivery (↑ perfusion). Hence, up to 90 % of CO is distributed to the skeletal muscles during heavy exercise [15]. Such a spectacular change cannot only be achieved by sympathetic cardiac activation (e.g., ↑ stroke volume, ↑ heart rate) but is rather mediated by the arteriolar vasodilation within the tissues (↓ resistance to blood flow) and the recruitment of capillaries [16].

Neither increasing blood flow nor arterial O2 content increases oxygen consumption in resting tissue [17]. When cells increase their metabolic activity, initially, blood flow is not adjusted to the greater oxygen demand. Inadequate flow impairs clearance of metabolic waste and induces local hypoxia that precipitates anaerobic metabolism [18]. These factors, together with various paracrine hormones and endothelial substances, induce vasodilation that enables more blood to enter capillaries (Table 1).

The vasodilatory magnitude differs between various factors and target vasculatures, e.g. in cerebral vessels, PCO2 (and H+) appears to have a detrimental effect on dilation [19]. Furthermore, there are some organ-specific mechanisms responsible for vasodilation, such as increased activity of GABAergic interneurons and increased glutamatergic excitation in the brain or myogenic autoregulation. In the latter, higher blood pressure (BP) stretches arteries, activating L-type calcium channels, resulting in vasoconstriction, whereas lower BP induces vasodilation in a reverse mechanism [18]. Thanks to autoregulation, tissue blood inflow can be maintained across different perfusion pressures. Myogenic autoregulation is most significantly expressed in critical vasculatures like cerebral or coronary arteries. In summary, vasodilation plays an important role in increasing tissue perfusion.

Adequate tissue perfusion relies on sympathetic nervous system (SNS) activity and circulating hormones (e.g. catecholamines, vasopressin and renin-angiotensin-aldosterone system). These are not typically involved in vascular vasodilation but are responsible for ascertaining the appropriate energy load of the circulating blood. For instance, when a person stands up quickly and experiences gravitational hypotension, baroreceptors in the aortic arch and carotid sinuses reduce tonic inhibition of the SNS. This reduction triggers reflex vasoconstriction and cardiac stimulation, maintaining adequate perfusion pressure to the cerebral vasculature and preventing fainting. Furthermore, venous vasoconstriction ascertains venous return and appropriate filling pressures to the right heart and CO [20]. Another systemic mechanism involves chemoreceptors in the carotid arteries and the medulla, which are sensitive to PO2, PCO2, and pH. Although their primary function is to regulate respiratory function, they also influence the cardiovascular system. Specifically, SNS activation increases systemic vascular resistance (SVR) and cardiac output (CO) in response to hypoxia, hypercarbia, and acidosis. Overall, the systemic response to hypotension aims to maintain perfusion pressure to the tissues, especially, to the brain. If the elevated pressure is to be converted to elevated flow, it can be achieved only if a sufficient gradient between arteriolas and venulas is maintained [21].

Table 1
Summary of substances inducing local vasodilation [15,18,103].

Factor	Substance	Effect
Metabolic factors	↓ PO2 (result of an increased oxygen demand)	● ↓ smooth muscle metabolic activity (↓ vascular contraction) ● ↑ activity of lactate dehydrogenase (↑ H+, ↑ lactate) ● ↓ aerobic metabolism (↑ adenosine) ● ↑ reduced heme, a cofactor for NOS (↑ NO)
	↑ PCO2 (metabolic waste, result of ↓ clearance and ↑ aerobic metabolism)	● ↑ local acidosis (↑ H+)
	↑ H+ (metabolic waste, result of decreased clearance + anaerobic glycolysis)	● ↑ NOS (↑ NO) ● ↑ activity of K+ channels (membrane hyperpolarization)
	↑ Lactate (metabolic waste, result of decreased clearance + anaerobic glycolysis)	● ↑ local acidosis (↑ H+)
	↑ Adenosine (↓ ATP formation, result of hypoxia)	● ↑ cAMP and the following decrease in intracellular calcium resulting in vasodilation ● ↑ NOS (↑ NO) ● ↑ PGI2 synthesis
	↑ K+ in the extracellular space (result of rapid depolarizations)	● membrane hyperpolarization (↓ vascular contraction)
Endothelium factors	↑ NO (result of ↑ shearing stress, ↑ pulsatile flow, ↓ PO2, bradykinin, acetylcholine)	● ↑ cGMP and the following ↓ intracellular calcium resulting in vasodilation ● ↑ PGI2 synthesis
	↑ EDHF (result of ↑ shearing stress, result of bradykinin, acetylcholine and histamine stimulation)	● ↑ activity of K+ channels (membrane hyperpolarization)
	↑ PGI2 (result of adenosine bradykinin, histamine, acetylcholine and NO stimulation)	● ↑ cAMP and the following decrease in intracellular calcium resulting in vasodilation
Paracrine factors	↑ histamine, ↑ substance P, ↑ bradykinin, ↑ acetylcholine (result of tissue injury, parasympathetic stimulation, inflammation and heat)	● ↑ NOS (↑ NO) ● ↑ PGI2 synthesis ● ↑ EDHF

Legend: PO2: partial pressure of oxygen; PCO2: partial pressure of carbon dioxide; ATP: adenosine triphosphate; NO: nitric oxide; NOS: nitric oxide synthase; cAMP: cyclic adenosine monophosphate; cGMP: cyclic guanosine monophosphate; PGI2: prostacyclin; EDHF: Endothelium-Derived Hyperpolarizing Factor.

3. Influence of anesthesia on tissue perfusion

General anesthesia (GA) is a pharmacologically induced state of unconsciousness and insensitivity to pain during a surgical procedure. One of the many effects caused by GA is depression of CVS: GA induction is often associated with hypotension, decreased SVR and CO. [22,23] Apart from the visible alteration of macrohemodynamic parameters, GA has also been observed to influence the interplay between tissue metabolism and perfusion.

First and foremost, anesthesia decreases oxygen demand of the tissues [17]. Although variously reported in the literature, it is reported that GA causes a decrease of around 25 % in energy expenditure, thereby reducing O_2 demand [24]. However, not all tissues decrease their O_2 demand by the same amount. It is speculated that the heart and lungs

experience the largest decrease in its metabolic activity, and thus, contribute the most to the overall change in the global VO2 [25–27]. Decreased oxygen demand could mean that lower perfusion is effective in maintaining effective oxygenation of the tissues.

GA (mostly with volatile anesthetics) is speculated to also modify local tissue perfusion. As documented in neuroanesthesia, VA decreases brain metabolism but increases cerebral perfusion (known as neurovascular uncoupling) [19]. Augmented perfusion is naturally mediated by vasodilation by: 1) ↑ NO and prostanoids production, 2) ↑ activity of K+ channels (membrane hyperpolarization) and 3) ↓ myogenic autoregulation (↑ arterial dilation) [19]. Hence, decreased metabolism is met with increased perfusion. It is then obvious why volatile anesthesia (VA) reduces cerebral reactivity to either hypo or hypercapnia - vasculature is already dilated [28]. Differently than in VA, total intravenous anesthesia (TIVA) with propofol is associated with maintained neurovascular coupling, where an intact, but lower oxidative metabolism mediates vasoconstriction and reduces cerebral flow [29]. Analogously, TIVA may blunt reactivity to vasoconstriction effects of hypocapnia [30]. Perfusion effects of anesthetics are also recognized in other organs. Indeed, both VA and TIVA have been observed to decrease vascular resistance [31,32]. For example, sevoflurane is known to improve flow through coronary and hepatic arteries via vasodilation. In a study by Takeda et al., hypotension induced by sevoflurane (50 % MAP decrease; 114 → 60 mmHg) resulted in a decreased organ blood flow, but not to a point of hypoperfusion which would result in acidosis or hyperlactatemia. Although MAP was decreased by 50 %, perfusion through the kidneys, liver and pancreas were affected by a smaller amount, highlighting the role of vasodilation in maintaining organ perfusion. Nevertheless, sevoflurane has also been linked to renal vasoconstriction - high concentrations are speculated to decrease local NO synthesis and increase renal sympathetic nerve stimulation [33,34].

Above considerations have been well summarized in an experimental study by Durieux et al., in which isoflurane-anesthetized rats were exposed to systemic hypoxia [35]. While in awake rats, hypoxia resulted in an effective drop in cerebral vascular resistance which increased brain perfusion, in isoflurane-anesthetized rats cerebral vasculature was already dilated and no significant dilation was further induced. It could be thus speculated that anesthetic agents exhaust vasodilatory mechanisms that should otherwise promote perfusion to the hypoxic tissues.

Regardless of modifications to regional blood flow, GA influences systemic hemodynamics [20]. Whether under VA or TIVA, sympathetic reflexes are attenuated by blocking neurotransmission in rostral ventrolateral medulla, a central regulator of SNS activity [36].

Both baro- and chemoreceptors, as well as adrenal glands are affected, which contribute to decreased levels of circulating catecholamines [37]. Thus, while anesthetized, any hypotension or hypoxemic events may not be appropriately managed by endogenous mechanisms (systemic vasoconstriction and cardiac stimulation), and thus need to be managed with exogenous interventions [38–42]. The question arises, whether these interventions, routinely guided by macrohemodynamics, accurately improve tissue perfusion.

4. Hemodynamic interventions and tissue perfusion

Each perioperative scenario is inherently a multi-complex entity where clinical decisions should be based on clear feedback and effective interventions. Despite the best efforts, the results of the largest randomized controlled trials (RCT) that focused on either GDT or attaining specific BP targets in perioperative populations varied from beneficial to harmful effects (Supplementary Table 1). Furthermore, pooled evidence regarding GDT and postoperative mortality provided imprecise estimates (50 trials; 5327 patients; OR 0.84; 95 %CI 0.64 to 1.09) [4], whereas evidence regarding BP targets did not favor higher BPs (12 trials; 10,250 patients; OR 1.10; 95 %CI 0.82 to 1.48) [2]. It should be highlighted that none of the trials measured tissue perfusion, as all hemodynamic interventions were dictated by macrohemodynamics.

4.1. Goal-directed therapy and tissue perfusion

For the majority of the GDT protocols, interventions were based on maximizing stroke volume, either via fluid administration up to fluid-unresponsiveness or by administering inotropes. It should be highlighted that fluid-responsiveness (FR) is a physiological state and is not synonymous with the actual individual fluid needs [43]. Just because a patient is in the steep part of the Frank-Starling curve (the physiological state of the normal heart), it is not equivalent with hypovolemia or hypoperfusion, and should not be regarded as a trigger for mandatory fluid infusion. Excessive infusion of fluids is associated with the risk of fluid congestion and overload, which poses risk to organ dysfunction [13]. Furthermore, administering inotropes which act to augment HR and myocardial contractility, inherently increase myocardial oxygen demand which could be deleterious by itself [44]. Not only that, inotropes often exhibit vasodilatory properties, affecting modulatory mechanisms of perfusion. In the recently published RCT (OPTIMIZE II trial), perioperative low-dose inotropes were associated with increased incidence of acute cardiac events, mainly tachyarrhythmias [45]. It can be speculated that GDT protocols may promote overtreatment via not adequately balancing the potential benefits of augmenting tissue perfusion with their associated harms (Fig. 1A). Furthermore, it remains unclear whether tissue perfusion is routinely increased by the GDT intervention, which would be necessary for GDT to improve outcomes.

4.2. Hypotension avoidance and tissue perfusion

The trials that focused on increasing perioperative BP have one thing in common: they mostly utilized vasopressors to reach the targets (Fig. 1B). The reasoning behind such an approach has been driven by observational evidence linking intraoperative hypotension (IOH) with postoperative complications. However, recent meta-analyses have failed to prove that reducing the incidence of IOH is indeed beneficial for survival [2,46]. These findings warrant further explanation.

Conventionally, MAP is the primary driver for tissue flow, as it is the main determinant of perfusion pressure (MAP-CVP). It should be noted however, that MAP is determined both by CO and SVR, and SVR is related to systemic vasoconstriction. Derived mainly from critical care studies, excessive vasoconstriction can compromise flow and induce tissue ischemia, especially under large doses [47–49]. Interestingly, this phenomenon has also been documented in perioperative populations. In one study (TIVA patients), administration of phenylephrine (alpha-1 agonist) due to IOH was associated with an increase in MAP but with a decrease of CO and cerebral oxygenation [50]. The authors speculated that phenylephrine-induced vasoconstriction of the cerebral vasculature contributed to a decreased blood flow to the brain (contrary to popular opinion, cerebral vessels have alpha-1 receptors which stimulate vasoconstriction [51]). The results of this study were also confirmed in experiments on healthy subjects, in which administration of norepinephrine was also associated with decreases in cerebral flow [52,53] and CO [52]. It could be hypothesized that vasopressors cause indiscriminate vasoconstriction, having the potential to negatively affect brain flow despite it being the most critical organ of the body. It also appears that any loss of vascular tone during anesthesia is not restored in the same proportions by the vasopressor [54], and may even interfere with the physiological vasodilation that normally acts to promote local tissue perfusion.

Above hypothesis could explain the recently emerged data on postoperative acute kidney injury (AKI). In a large, 5-year retrospective study from the US, an increasing trend for perioperative use of vasopressors (and a decrease in fluids) was associated with an increased incidence of AKI [55]. Importantly, that happened despite significantly reducing the duration of IOH. Parallel results were also obtained in a large RCT (the RELIEF trial), in which the restrictive fluid strategy group received more vasopressors than patients assigned to a more liberal fluid dosing [56]. Although no causality was demonstrated, it could be

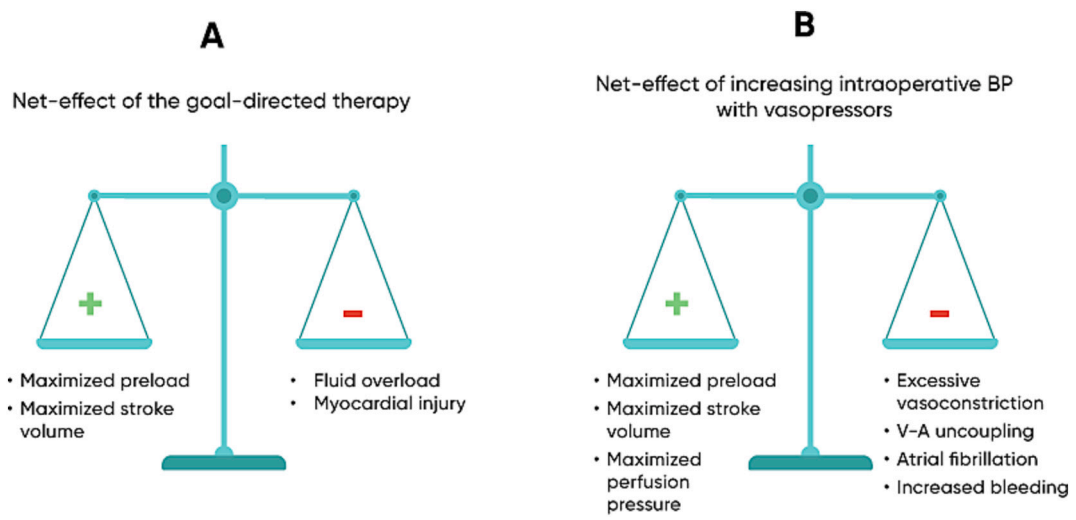

Fig. 1. Theoretical net-effect of the goal-directed therapy and increasing blood pressure intraoperatively. V-A uncoupling: ventriculo-arterial uncoupling: an increase in arterial elastance can impede effective left ventricular contraction, leading to a decrease in stroke volume.

speculated that an unselected vasopressor use contributes to vasoconstriction of renal vasculature (renal vessels are highly saturated with alpha-1 receptors [57]) and, in that way, compromise renal function [58]. Indeed, norepinephrine use has been linked with worsening renal perfusion, although such an effect may depend on the underlying condition [59,60]. Thus, one can speculate that induced vasoconstriction is one of the culprits of perioperative AKI [61]. An analogous issue was observed in hepatic blood flow (HBF) in patients under GA with the adjunction of thoracic epidural anesthesia [62]. In that study, norepinephrine administered due to IOH (MAP <60 mmHg) further compromised HBF, despite increasing MAP. Furthermore, in a study in ICU patients with traumatic brain injury, MAP uptitration with a vasopressor produced distinct brain tissue oxygenation (PbtO2) responses, including decreased PbtO2 [63]. To sum up, there is variable effect of MAP uptitration on perfusion, and cannot be predicted based solely on the macrohemodynamic parameters [64].

Irrespective of the possibly deleterious effects of vasopressors, it is not debatable that their use is crucial in restoring CV stability and, thus, tissue perfusion. For example, vasopressors are a rational choice to prevent severe hypotension in case of cardiac surgery-related vasoplegia [65] or to ascertain appropriate perfusion pressure for the right coronary artery. It is clear that in some specific populations and conditions

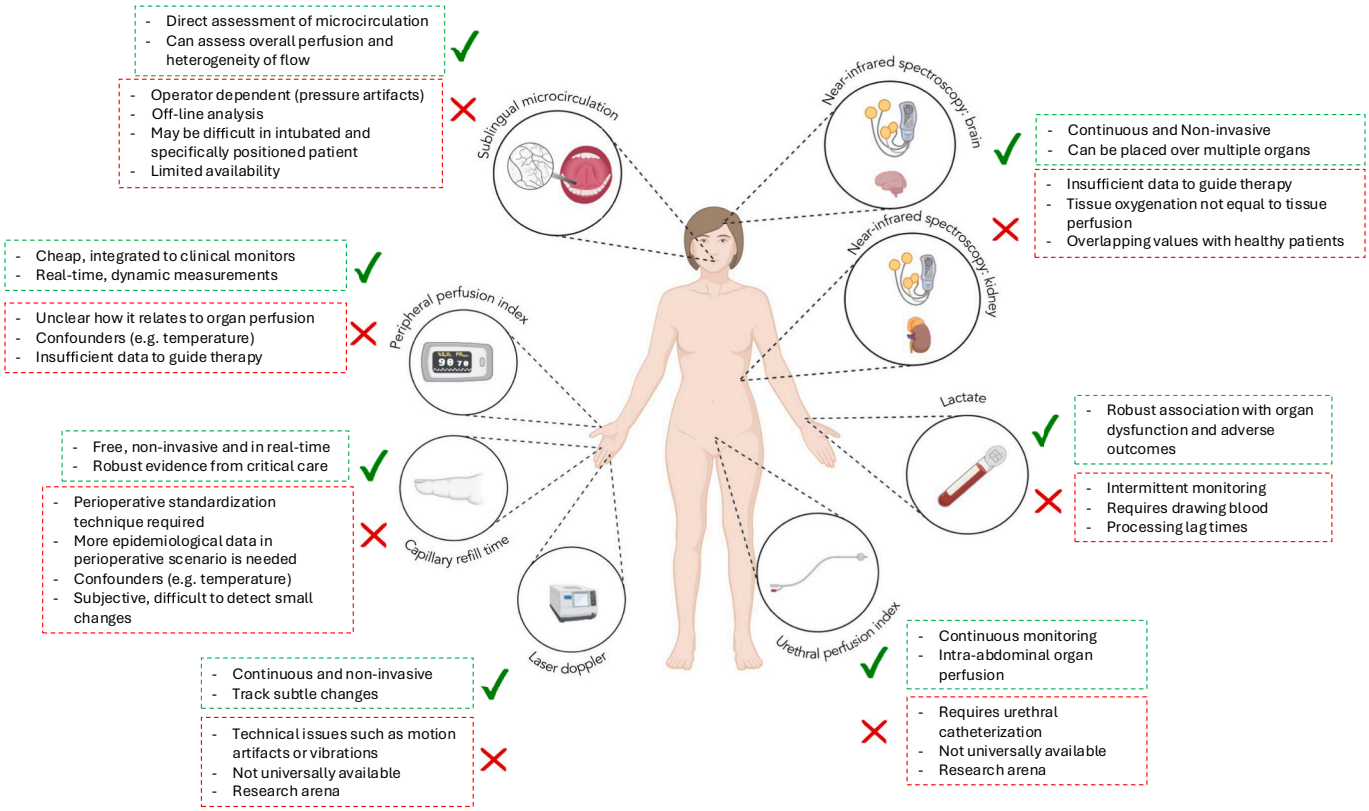
- Direct assessment of microcirculation
- Can assess overall perfusion and heterogeneity of flow
- Operator dependent (pressure artifacts)
- Off-line analysis
- May be difficult in intubated and specifically positioned patient
- Limited availability
Sublingual microcirculation
Near-infrared spectroscopy- brain
- Continuous and Non-invasive
- Can be placed over multiple organs
- Insufficient data to guide therapy
- Tissue oxygenation not equal to tissue perfusion
- Overlapping values with healthy patients
Near-infrared spectroscopy- kidney
- Cheap, integrated to clinical monitors
- Real-time, dynamic measurements
- Unclear how it relates to organ perfusion
- Confounders (e.g. temperature)
- Insufficient data to guide therapy
Peripheral perfusion index
Lactate
- Robust association with organ dysfunction and adverse outcomes
- Intermittent monitoring
- Requires drawing blood
- Processing lag times
- Free, non-invasive and in real-time
- Robust evidence from critical care
- Perioperative standardization technique required
- More epidemiological data in perioperative scenario is needed
- Confounders (e.g. temperature)
- Subjective, difficult to detect small changes
Capillary refill time
Laser doppler
Urethral perfusion index
- Continuous monitoring
- Intra-abdominal organ perfusion
- Requires urethral catheterization
- Not universally available
- Research arena
- Continuous and non-invasive
- Track subtle changes
- Technical issues such as motion artifacts or vibrations
- Not universally available
- Research arena

Fig. 2. Possible windows for tissue perfusion monitoring.

vasopressors have beneficial effects. But, how to identify who might benefit from a vasopressor and when? Firstly, there should be indicators of impaired tissue perfusion thought to be of vasodilatory origin. Importantly, even if there is a drop in MAP, it may not always be associated with hypoperfusion. Secondly, vasoconstrictive effects shouldn't outweigh the local vasodilatory mechanisms, as tissue flow is then less likely to be improved. Thirdly, it would be best if a vasopressor recruited the venous compartment which would then increase venous return and filling pressures and CO. [66–69] In short, stressing volume and increasing mean systemic filling pressure, not just increasing MAP, is an important role of a vasopressor.

5. Tissue perfusion monitors

The missing link to implementing the tissue perfusion monitoring into clinical practice is, of course, the lack of an easily accessible, validated and fully-understood tissue perfusion monitor in the perioperative scenario. While there are several direct and indirect options, none of them has strong evidence to support its use today (Fig. 2).

5.1. Near-infrared spectroscopy (NIRS)

NIRS is a non-invasive method to measure tissue oxygenation in organs such as brain, kidneys or muscles. It uses near-infrared light to assess oxygen levels by measuring absorption by oxygenated and deoxygenated hemoglobin in blood vessels. The advantages of this method include its non-invasive approach, real-time dynamic measurements, and its ability to estimate oxygenation levels in target tissues. As for the disadvantages, NIRS measurements can be confounded by temperature or signals coming from the outer layer structures (e.g. skin). Furthermore, the technique is costly and is not universally available.

The use of NIRS enables to observe relationship between macrohemodynamic interventions and their effect on target tissue oxygenation. Several papers have already explored this issue, highlighting that the level of tissue oxygenation is often disconnected from improvements tissue perfusion proxies, such as BP. For example, in healthy subjects, increasing MAP with norepinephrine (0.1 μg/kg/min) has led to significant decrease in NIRS-derived brain oxygenation [53]. Furthermore, in anesthetized patients requiring upright position, cerebral oxygenation decreased despite maintaining MAP with phenylephrine [70]. In one, small RCTs on patients undergoing carotid endarterectomy, strategy aimed at optimizing brain oxygenation measured by NIRS was found to be related with lower vasopressor use and lower rate of perioperative complications [71]. Lastly, in patients undergoing cardiac surgery with cardiopulmonary bypass (CBP), maintaining MAP of 80 mmHg with varying norepinephrine doses was not associated with any significant changes in brain oxygenation [72]. Apart from assessing brain oxygenation, kidney NIRS was also shown to correlate well with invasively measured renal venous oxygen saturation [73]. In anesthetized piglets, higher doses of norepinephrine or epinephrine had a deleterious effect on renal oxygenation [74].

Although NIRS has been increasingly adopted in the perioperative care, there remains a lack of evidence supporting its effectiveness in guiding interventions to improve postoperative outcomes. A recent large single-center randomized controlled trial involving 1960 participants found that while patients in the NIRS-guided group had improved cerebral oxygenation compared to those in the conventional care group, this did not translate into a reduction in composite postoperative complications (RR 0.99; 95 %CI, 0.90 to 1.08;), P = 0.83 [75]. Whether this outcome reflects the limited efficacy of NIRS itself or shortcomings in the intervention protocol remains uncertain.

5.2. Peripheral perfusion index (PPI)

PPI is a numerical value indicating the pulsatile proportion of blood flow that is measured by pulse oximeters on the patient's extremities, such as the fingers. If the high PPI describes an increased blood inflow to the arterioles (greater blood influx due to reduced resistance), the low PPI describes the opposite [76]. The strengths of PPI include its non-invasive nature, real-time recording capability, cost-effectiveness, and the convenience of measurement using standard pulse oximeters. As for the cons, it remains unclear how PPI values reflect internal organ perfusion, and, PPI could be confounded by the temperature effect on skin blood flow. Finally, PPI values often exhibit a wide range of values in healthy volunteers which can make interpretation of measurements difficult. Nevertheless. PPI values correspond with other markers of peripheral perfusion (e.g. core-to-toe temperature difference) [77].

Although not extensively studied, higher intraoperative PPI was numerously associated with improved outcomes [78,79]. Interestingly, PPI closely followed macrohemodynamic changes induced by preload decrease. The recent results of the Krone's study showed that lower PPI was better associated with AKI than IOH based on MAP [79]. Furthermore, in a mixed cohort of surgical patients, higher post-induction PPI was associated with attenuated cardiovascular compromise, with lower decreases in stroke volume [76]. In the same line as with the NIRS technology, at the moment, PPI has proven useful to identify patients at risk of adverse event, yet no study has targeted it as and resuscitation endpoint and compared outcomes in an interventional protocol.

5.3. Lactate

Lactate, being a normal product of glucose and pyruvate breakdown, is often elevated as anaerobic metabolism is triggered by tissue hypoperfusion. Higher intraoperative lactate concentrations have been reported to correlate with worse outcomes [80–82]. Their dynamics may reflect a metabolism switch from aerobic to anaerobic, which indicates significant hypoperfusion. However, a delay exists between the onset of hypoperfusion and the subsequent rise in lactate levels, potentially postponing timely intervention. Similarly, the slow kinetics of recovery of lactate even after a successful macrohemodynamic optimization makes it an unreliable monitor to assess the response of tissue perfusion to frequent interventions such as fluid challenge or vasopressor adjustments.

Additionally, repetitive lactate measurements expose patients to numerous blood samplings. Lastly, lactate measurements can be confounded by non-hypoperfusion phenomena, such as an impaired hepatic lactate clearance or stress-related adrenergic glycolysis [83].

5.4. Capillary refill time (CRT)

CRT is a simple and a costless tool that measures skin blood flow and microvascular reactivity. It can be measured in various locations, including finger, earlobe or the knee [84]. As CRT was validated as a marker of reperfusion in shock, optimizing CRT has become risk signal and a reliable hemodynamic target in critically ill patients [85]. Moreover, prolonged CRT corresponds with the level of organ failure [86].

In the intraoperative scenario, CRT's behavior is not yet fully understood, hence its perioperative role remains to be determined. Also, assessing CRT in the fingertip, which has the most widely studied, could be challenging due to surgical positioning. Nevertheless, it has been shown that CRT improves after induction of anesthesia, despite a decrease in MAP (attributed mostly to sympatholysis) [87]. Indeed, such an increase in skin perfusion has been speculated to promote perioperative hypothermia [88]. It remains unknown how intraoperative CRT corresponds with perfusion of other organs, however, knowing that GA induces vasodilation and improves skin perfusion, prolonged CRT could be a marker of tissue hypoperfusion. Despite the lack of robust intraoperative evidence, an immediate abnormal capillary refill time after major surgery predicted postoperative complications in one study [89]. An important fact to be considered is the rapid kinetics of response of CRT to macrohemodynamic optimization, for instance, with fluid boluses, where some studies in septic shock have shown an improvement in

minutes after the intervention. This could be very relevant in the intraoperative theater.

Considering that this technique is costless and non-invasive, it could become a promising perioperative perfusion monitoring tool, that could seamlessly be integrated into daily clinical practice once future studies provide more physiological and clinical data in this setting.

5.5. Laser doppler flowmetry (LDF)

LDF is a light-emission based technique that measures doppler shift of red blood cell movement in the tissue surface. Usually applied on the skin, it is a non-invasive method that gathers blood flow signal from the microvessels and is sensitive to dynamic changes.

Mostly studied in critical care, LDF has been proven to be an effective way to observe tissue flow changes induced by interventions. In one study, LDF was shown to be effective in detecting flow improvements after fluid bolus [90]. Low skin blood flow measured by LDF was also found to be prognostic of mortality in shock patients [91]. Even though LDF could be seen as a promising and emerging technology due its' physiological background, continuous signal and rapid changes to hemodynamic interventions, the technique currently has several limitations. Among them we can highlight the impact of tissue optical properties on the perfusion signal, motion artifacts, absence of quantitative perfusion units, limited measurement depth (~1 mm), and the lack of "biological zero" signal (perfusion measured under no-flow conditions) [92]. Therefore, it has mainly been restricted to the research arena.

5.6. Urethral perfusion index (uPI)

uPI is a pulse oximetry derivative (similar to PPI), obtained by a dedicated sensor located within urinary catheter. uPI enables to register blood flow intensity through the microvasculature of the wall of the urethra. It appears to be well tolerated and have a good signal quality [93]. In one small RCT on patients undergoing liver surgery, it was found that goal-directed fluid therapy was able to produce higher uPI values compared with patients allocated to a standard group [94]. In another study, uPI has been found to be independent of CO, MAP and HR in patients undergoing CABG [95]. Whether uPI could be used as a target for interventions, remains to be determined.

5.7. Sublingual microcirculation assessment

Sublingual microcirculation assessment is a technique performed by using a hand-held vital microscope that utilizes dark-side field or dark-incident field imaging. They allow for a direct and noninvasive view of sublingual capillary bed. Hand-held vital microscopes obtain images of microvessels up to a diameter of 5 μm, including arterioles, capillaries, and venules. Several methods to categorize abnormalities were proposed, including scoring of microcirculatory flow, perfused vessel density and heterogeneity [96]. Furthermore, a number of studies demonstrated the adverse prognosis associated with persistent abnormalities particularly in the setting of septic shock [97].

However, short exposure time of patients to GA during elective major surgery make it unlikely that this kind of abnormalities are observed in this setting. In addition, this technique has been recently criticized because of several reasons. Among them, the inability to distinguish between adaptative versus maladaptive microcirculatory abnormalities, the inherent technical drawback of pressure artifacts with the videomicroscope that jeopardize interpretation of changes, the fact that it is an expensive and research-restricted technology with poor recent technological developments, and the lack of any proof that targeting sublingual microcirculatory abnormalities may be associated with better outcomes. Furthermore, it requires skilled operators and as the measurements are susceptible to subjectivity and obtaining reliable observations can be logistically challenging in intubated patients or those positioned in specific ways during surgery.

Despite the above, some data have been published in the perioperative setting. In surgical patients, it was shown that the induction of GA reduced sublingual capillary red blood cell flow but increased capillary vessel density [98]. Such a change did not lead to overall change in sublingual capillary flow and was not indicative of hypoperfusion. Importantly, norepinephrine therapy to treat IOH had no effect on microcirculation [99]. Furthermore, in an RCT that randomized patients to a strategy of cardiac index optimization (via larger fluid administration) did not lead to improved sublingual microcirculation when compared to a standard group [100]. However, in one study, in preload-dependent patients with decreased microcirculatory perfusion, administrating 500 mL of fluid bolus corrected the proportion of perfused vessels [101]. In another RCT, sublingual microcirculation was sensitive to different hemodynamic strategies [102].

To summarize, sublingual monitoring is far from being considered as a promising intraoperative monitor because of the reasons provided above.

6. Applying tissue perfusion monitoring in the perioperative scenario

If one were to dictate hemodynamic interventions based on the concepts described above, such an approach would have three pillars:

1) Any benefit of a hemodynamic intervention should be leveraged with its possible harm
2) Hemodynamic interventions are only needed when tissue perfusion is compromised, regardless of individual characteristics of a patient, e.g. hypertension or chronic heart failure
3) Successful hemodynamic intervention is defined as improving tissue hypoperfusion (relative to the baseline) and not only improving macrohemodynamic parameters

In practice, implementing these concepts would require adding an additional step to hemodynamic algorithms. In this approach, tissue hypoperfusion would first be diagnosed, followed by hemodynamic profiling to guide targeted interventions aimed at enhancing blood flow (Fig. 3). This concept could be evaluated in future trials. Furthermore, we hypothesize that it is PPI that could hold significant promise as a tissue perfusion monitor due to its affordability, widespread availability, non-invasiveness, and dynamic nature—features that make it easily integrable into hemodynamic algorithms. However, several critical aspects would first require further investigation: the optimal threshold for clinical intervention needs to be established; additional epidemiological data are needed to clarify the relationship between low PPI and postoperative complications; and importantly, the correlation between PPI and organ-specific perfusion—particularly in the brain and kidneys—must be explored.

7. Conclusions

Various physiological and pharmacological nuances influence tissue blood flow in way that challenge the commonly accepted therapeutic paradigms centered around macrohemodynamics. Implementation of tissue perfusion monitoring could be the missing link between hemodynamic interventions and their effect in improving perioperative outcomes. Tissue perfusion may be the ultimate target for perioperative hemodynamic therapy.

CRediT authorship contribution statement

Zbigniew Putowski: Writing – review & editing, Writing – original draft, Visualization, Conceptualization. **Jan Bakker:** Writing – review & editing, Writing – original draft. **Eduardo Kattan:** Writing – review & editing, Writing – original draft. **Glenn Hernández:** Writing – review &

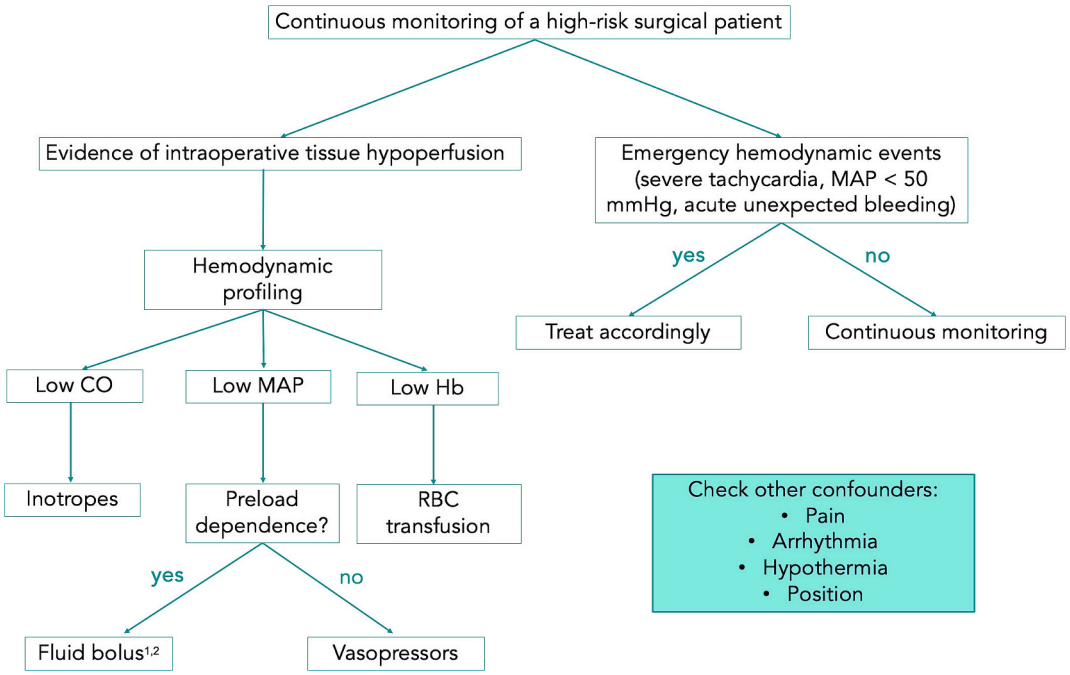

Fig. 3. Tissue perfusion assessment as the element of intraoperative hemodynamic algorithm. CO: cardiac output; MAP: mean arterial pressure; Hb: hemoglobin; RBC: red blood cells. [1] A fluid bolus will only improve MAP if arterial elastance is preserved. This can be assessed using dynamic arterial elastance (Eadyn). If arterial elastance is low, an increase in SV may not lead to a meaningful rise in MAP [2]; In cases where DAP is very low, consider initiating vasopressor therapy first." (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

editing, Writing – original draft. **Hafid Ait-Oufella:** Writing – review & editing, Writing – original draft. **Wojciech Szczeklik:** Writing – review & editing, Writing – original draft. **Philippe Guerci:** Writing – review & editing.

Funding sources

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

We thank Małgorzata Maraszewska for graphical editing of the figures.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jclinane.2025.112009.

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Glossary

GDT: goal-directed therapy
CO: cardiac output
DO2: oxygen delivery
CVS: cardiovascular system
BP: blood pressure
SNS: sympathetic nervous system
SVR: systemic vascular resistance
GA: general anesthesia
VA: volatile anesthesia
TIVA: total intravenous anesthesia
MAP: mean arterial pressure
FR: fluid responsiveness
AKI: acute kidney injury
RCT: randomized controlled trial
NIRS: near-infrared spectroscopy
CBP: cardiopulmonary bypass
PPI: peripheral perfusion index
SM: sublingual microcirculation
LDF: laser doppler flowmetry
uPI: urethral perfusion index
CRT: capillary refill time